

(19) World Intellectual Property
Organization
International Bureau



27 SEP 2004



(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 2003/087818 A3

(51) International Patent Classification⁷: **C07K 14/705**,
G01N 33/574, A61K 38/17, 31/7088, 39/395, C12Q 1/68,
C07K 16/28, A61P 3/00, 19/00, 13/12, 27/02

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(21) International Application Number:
PCT/EP2003/003277

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(22) International Filing Date: 28 March 2003 (28.03.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02 008 650.0 17 April 2002 (17.04.2002) EP

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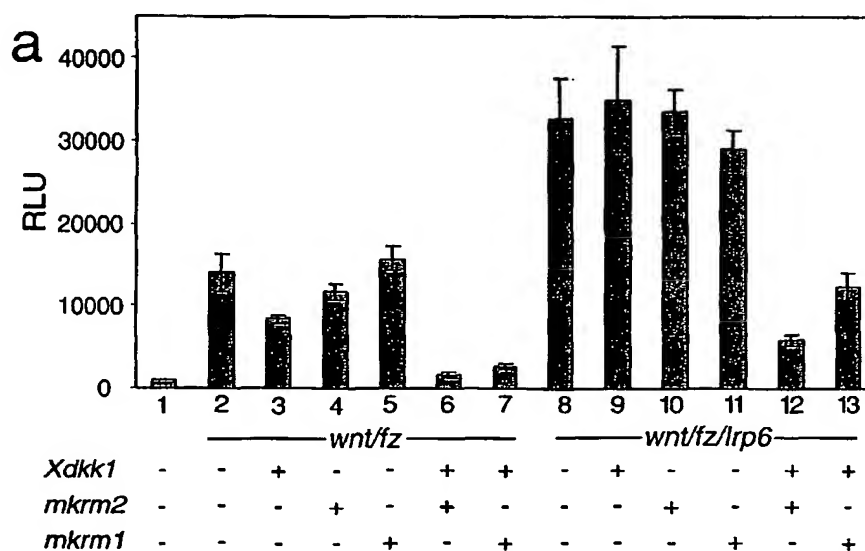
(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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[Continued on next page]

(54) Title: DIAGNOSTIC AND THERAPEUTIC USE OF KREMEN 1 AND 2, INHIBITORS OF THE CANONICAL WNT-SIGNALTRANSDUCTION



(57) Abstract: The present invention relates to a composition useful for the diagnosis and therapy of diseases associated with aberrant expression of the gene encoding the receptor Kremen 1 and/or Kremen 2 e.g. tumors or diseases of the kidneys, bones and eyes, lipid and glucose metabolism and obesity. The present invention also relates to a pharmaceutical composition containing a compound which is capable of modifying (a) the expression of the gene encoding Kremen 1 and/or Kremen 2 or (b) the activity of the Kremen 1 and/or Kremen 2 receptor.

WO 2003/087818 A3



Published:

— *with international search report*

(88) Date of publication of the international search report:

5 February 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03277

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/705 G01N33/574 A61K38/17 A61K31/7088 A61K39/395
C12Q1/68 C07K16/28 A61P3/00 A61P19/00 A61P13/12
A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EMBASE, EPO-Internal, WPI Data, PAJ, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VAN ES JOHAN H ET AL: "You Wnt some, you lose some: Oncogenes in the Wnt signaling pathway." CURRENT OPINION IN GENETICS & DEVELOPMENT, vol. 13, no. 1, 20 February 2003 (2003-02-20), pages 28-33, XP002249368 ISSN: 0959-437X page 30 -page 31 ----- -/--	11, 14, 18-20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

22 September 2003

Date of mailing of the international search report

14/10/2003

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BROWN SHERYL D ET AL: "Isolation and characterization of LRP6, a novel member of the low density lipoprotein receptor gene family." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 248, no. 3, 30 July 1998 (1998-07-30), pages 879-888, XP002249367 ISSN: 0006-291X the whole document	11,14, 18-20
X	NAKAMURA T ET AL: "Molecular cloning and characterization of Kremen, a novel kringle-containing transmembrane protein" BIOCHIMICA ET BIOPHYSICA ACTA, AMSTERDAM, NL, vol. 1518, no. 1-2, 19 March 2001 (2001-03-19), pages 63-72, XP002211811 ISSN: 0006-3002 the whole document	1,2,4-7, 10
X	US 2001/036643 A1 (HOLLOWAY JAMES L) 1 November 2001 (2001-11-01) abstract; claims 1-4 paragraph '0266! - paragraph '0268! paragraph '0230! - paragraph '0233! paragraph '0235! - paragraph '0245!	1-7,10, 15-18
X	EP 0 911 399 A (SMITHKLINE BEECHAM CORP) 28 April 1999 (1999-04-28) paragraph '0064! - paragraph '0067!; claims 1-7	1-20
X	DATABASE EMBL 'Online! 26 June 2001 (2001-06-26) retrieved from EBI Database accession no. AAB95341 XP002249432 abstract	1,2,4-7, 10
X	-& EP 1 074 617 A 7 February 2001 (2001-02-07) claim 8	1,2,4-7, 10
X	DATABASE EMBL 'Online! 6 November 2001 (2001-11-06) retrieved from EBI Database accession no. AAM93480 XP002249370 abstract	1,2,4-7
X	-& EP 1 130 094 A (HELIX RES INST) 5 September 2001 (2001-09-05) claim 8	1,2,4-7

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 02 066509 A (GENENTECH INC) 29 August 2002 (2002-08-29) the whole document	15-18
X	BAFICO A ET AL: "NOVEL MECHANISM OF WNT SIGNALLING INHIBITION MEDIATED BY DIKKOPF-1 INTERACTION WITH LRP6/ARROW" NATURE CELL BIOLOGY, MACMILLAN PUBLISHERS, GB, vol. 3, July 2001 (2001-07), pages 683-686, XP002952909 ISSN: 1465-7392 the whole document	15-18
X	MAO BINGYU ET AL: "LDL-receptor-related protein 6 is a receptor for Dickkopf proteins." NATURE (LONDON), vol. 411, no. 6835, 2001, pages 321-325, XP002249369 ISSN: 0028-0836 the whole document	15-18

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP 03/03277

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: —
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

Continuation of Box I.2

Present claims 11,14 and 16-21 relate to diseases defined by reference to their supposed cause, namely to be associated with an aberrant expression of kremen 1 or 2. Similarly, refers claim 22 to a process supporting regeneration.

Present claims 15-22 relate furthermore to compositions and compounds defined only by reference to the following result to be achieved, namely to modulate kremen 1 or 2 (gene or protein).

Claims 15, 18 and 21 finally refer to compounds, which are only defined by the characteristic, that they bind to kremen 1 or 2.

The claims cover all diseases and compounds/ compositions having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such diseases and compounds/ compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the diseases and compounds/ compositions by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for the following parts of the claims:

colon cancer, melanoma and breast cancer
diseases due to renal fibrosis
diseases due to aberrant lipid/ glucose metabolism
high bone disease and osteoporosis-pseudoglioma
tissue repair

compounds/ compositions modulating kremen: kremen 1 and 2 (gene and protein), hybridizing nucleotide sequences and antibodies, because these are the only modulators, which are supported by the description (p12).

binding partners of kremen 1 or 2: dkk 1 and 2, LRP6

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Form PCT/ISA/210 (patent family annex) (July 1992)